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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,706	02/09/2004	Lester F. Lau	05031.0008.NPUS01	2022

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HOWREY SIMON ARNOLD & WHITE LLP

Attention: Patent Administrator

Box No. 34

1299 Pennsylvania Avenue, N.W.

Washington, DC 20004-2402

EXAMINER

POPA, ILEANA

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/774,706	<b>Applicant(s)</b> LAU, LESTER F.	
	<b>Examiner</b> Ileana Popa	<b>Art Unit</b> 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.  
4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-21 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 09 February 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. ____.  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____.  | 6) <input type="checkbox"/> Other: ____.                                    |

### **DETAILED ACTION**

1. Claims 1-21 are pending.

#### ***Oath/Declaration***

The oath or declaration is defective. The oath or declaration is defective because the date when Applicant signed the Oath/Declaration is missing. Correction is required.

#### ***Claim Rejections - 35 USC § 112 – written description***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 8, 9, 19, and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1 "Written Description Requirement" makes it clear that the written description requirement for a claimed genus may be satisfied through sufficient

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description of a representative number of species disclosures of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3<sup>rd</sup> column).

When the claim is analyzed in light of the specification, the suspected modulator of effects associated with congenital heart disease can be any compound that has the ability to alter the phenotype, as compared to the control (p. 6, paragraph 0023). It is noted that the specification does not disclose any detected modulator that is able to modulate the claimed phenotype or any other possible phenotype associated with CCN1 disruption. Therefore the detected modulator is not particularly limited by its structure or mode of action. The genus, i.e., the detected modulator, is described by its function to alter phenotype, but the specification does not provide any disclosure as to what would have been the complete structure of sufficient number of species of the claimed genus. Additionally, the specification does not describe what would have been the identifying characteristics, such as specific features and functional attributes, of the different detected modulators. It is acknowledged that there is no art that provides examples of agents that can modulate a phenotype associated with CCN1 gene disruption.

In conclusion, this limited information is not sufficient to reasonably convey to one of ordinary skills in the art that the Applicants invented what was claimed.

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Consequently, the Applicants were not in possession of the instant claimed invention, at the time the application was filed.

***Claim Rejections - 35 USC § 112 – enablement***

4. Claims 19 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC § 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skills of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The instant claims are drawn to a method of identifying a modulator of symptoms associated with atrioventricular septal defects comprising contacting a CCN<sup>+/-</sup> mouse with a suspected modulator and measuring the effect that the suspected modulator has on the phenotype associated with atrioventricular septal defects in comparison to the

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control. In order to measure this effect, the phenotype of the  $CCN^{+/-}$  mouse must be determined prior and after contacting the mouse with the suspected modulator. However, in the absence of the evidence to the contrary, there is no *in vivo* test to determine whether a  $CCN^{+/-}$  mouse comprises the claimed atrioventricular septal defects. It is noted that the art discloses that the genetic mouse models for cardiovascular diseases are still awaiting for the development of suitable methods to characterize their phenotype, i.e., the necessity to miniaturize and refine the techniques currently used in larger animals; only these allow for the determination of the cardiovascular phenotypes in the intact, conscious mice (Fitzgerald SM et al, Clin Exp Pharmacol Physiol, 2003, 30: 207-216). The specification discloses only determining the phenotype for the  $CCN^{+/-}$  mice by histological analysis of dead animals and therefore, those animals cannot be used in further studies. Therefore, it is not clear how the beneficial effect that a suspected modulator has on the claimed phenotype can be determined without a starting point, i.e., the phenotype of the untreated mouse.

Given these facts, the skilled artisan would not know *a priori* whether the using of a suspected modulator result in altering the phenotype of the  $CCN^{+/-}$  mice as compared to the control. One of skill in the art would not know how to determine if a suspected modulator is capable to change the phenotype of the mice in question. The specification would need to describe examples that specifically address the *in vivo* determination of the phenotype for the same animal before and after contacting the animal with the test substance. Thus, the specification is not enabling for the claims drawn to a method of identifying a modulator of symptoms associated with

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atrioventricular septal defects comprising contacting a CCN<sup>+/-</sup> mouse with a suspected modulator and measuring the effect that the suspected modulator has on the phenotype associated with atrioventricular septal defects in comparison to the control, i.e., claims 19 and 29.

***Claim Rejections - 35 USC § 102***

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-7 and 10-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Mo et al. (Mol Cell Biol, 2002, 22: 8709-8720).

Mo et al. teach a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise heterozygous or homozygous disruptions of the CCN1 gene, and testing the transgenic mice for their genotype (p.8710, column 2, bridging p.8711, Table 1). Mo et al. do not mention the phenotype of the heterozygous mice. However, in the absence of evidence to the contrary, the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed atrioventricular septal defects or a predisposition to atrioventricular septal defects, i.e., the phenotype is inherent to the transgenic mice comprising a heterozygous disruption in the CCN1 gene. With respect to the limitation of testing the heterozygous transgenic mice for a phenotype associated with atrioventricular septal

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defects, Mo et al. teach analyzing  $\beta$ -galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry (p. 8710, column 2, second paragraph), which would necessarily have resulted in the determination of such a prominent phenotype associated with atrioventricular septal defect. With respect to the limitation of a homogeneous population of transgenic mice with a heterozygous disruption in CCN1, Mo et al. teach a population of 225 viable CCN<sup>+/-</sup> mice (p. 8710, column 2, third paragraph).

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. Claims 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mo et al., in view of Christensen et al. (Am J Ophysiol, 1977, 272: H2513-2524) and Bruneau et al. (Cell, 2001, 106: 709-721), as evidenced by Hickey et al. (Cytogenet Genome Res, 2003, 100: 276-286).

Mo et al. teach transgenic mice whose genome comprises a heterozygous disruption of the CCN1 gene (see above). Mo et al. do not teach using these in a method of identifying a modulator of symptoms associated with atrioventricular septal defects. However, prior to the time that the claimed invention was made, Christensen et al. taught that mouse models of heart disease may serve to develop appropriate



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therapeutic strategies for human heart diseases (Abstract). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to use the mice of Mo et al. to screen for potential modulators of atrioventricular septal defects, with a reasonable expectation of success. The motivation to do so is provided by Bruneau et al., who teach that heterozygous mice models for congenital heart disease can be used to understand the pathway that leads to the development of the disease and to identify factors that could modify this pathway, i.e., factors that can alter the phenotype associated with congenital heart disease (p. 719, column 2, Conclusions). One of skill in the art would have had a reasonable expectation of success in using such a method because it has been shown that mice can be used as models of human diseases to identify agents that can modify the phenotype associated with those diseases (see Hickey et al., p. 283, column 1, second paragraph). Thus the claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

It is emphasized that this 103 rejection is not inconsistent with the enablement rejection. The combined teachings of Mo et al, Christensen et al., and Bruneau et al. descriptively disclose the instant rejection, however, they do not enable the instant invention for the reasons given above. The desire of those of ordinary skill in the art to obtain evidence for the function of genes and identify factors that could alter the pathways in which these genes are involved was well established at the time of filing. The mere fact that those of skill in the art would have had desired to use knockout mice to identify factors that can modulate the claimed phenotype associated does not necessarily mean that the method would have had been enabled, i.e., those of skill in

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the art would have had identified modulators of claimed phenotype by using the instant knockout mice in the instant method. Evidence to support this is provided by Applicant who, although they obtained CCN1 knockout mice, did not provide agents that can modulate the phenotype associated with the disruption of this gene.

Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mo et al., in view of both Mah et al. (Genet Test, 1999, 3: 157-172) and Ciarleglio et al. (J Clin Invest, 2003, 112: 1280-1286).

Mo et al. teach transgenic mice whose genome comprises a heterozygous disruption of the CCN1 gene (see above). Mo et al. do not teach a method of identifying an animal that is predisposed to atrioventricular septal defects by testing the DNA isolated from the animal for the presence of an alteration in one or more alleles of the CCN1 gene. However, prior to the time that the claimed invention was made, Mah et al. taught genetic testing for cardiac disorders (Abstract). It would have been obvious to one of ordinary skill in the art, at the time the invention was made, to identify predisposition to atrioventricular septal defects by testing the DNA obtained from subjects for mutations in the CCN1 gene, with a reasonable expectation of success. The motivation to do so is provided by Mo et al., who teach that disruption of CCN1 function plays a role in the development of atrioventricular septal defects (see above), and by Ciarleglio et al., who teach the benefits of genetic testing to identify predisposition to genetic disorders (p. 1285, column 3). One of skill in the art would have had a reasonable expectation of success in using such a method because genetic

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testing was successfully used to identify predisposition for various genetic disorders, among which congenital heart disease (see Ciarleglio et al., p. 1281, column 2, last paragraph). Thus the claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

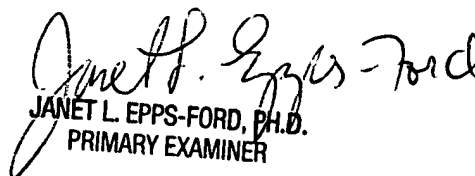
9. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ileana Popa

  
JANET L. EPPS-FORD, PH.D.  
PRIMARY EXAMINER